75. (new) The method of claim 57, wherein the KDEL receptor inhibitor protein is encoded by a nucleotide sequence selected from the group consisting of: SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, and SEQ ID NO:35.--

5 Cont

Remarks

Prior to this Amendment, claims 20-37 were pending. By this Amendment, claims 27 and 36 have been canceled, claims 20-26, 28-35, and 37 have been amended, and new claims 44-75 have been added. Therefore, after this Amendment is entered, claims 20-26, 28-35, 37, and 44-75 will be pending.

As described below, the amendments to claims 20-26, 28-35, and 37 are fully supported in the specification. New claims 44-75 are fully supported in the specification. Accordingly, no new matter has been introduced by these amendments and these new claims.

Claim 20 has been amended to recite that:

- the ligand sequence comprises the amino acid sequence X-Asp-Glu-Leu at the carboxy terminus of the protein. Support for this limitation is found in the specification at page 11, lines 24-27.

- the KDEL receptor inhibitor is a protein. Support for this limitation is found in the specification at page 5, lines 11-14.

- the KDEL receptor inhibitor protein comprises the amino acid sequence X-Asp-Glu-Leu located at the carboxy terminus of the KDEL receptor inhibitor protein. Support for this limitation is found in the specification at page 11, lines 24-27.

Claims 21 and 30 have been amended to recite that each subunit has the the amino acid sequence X-Asp-Glu-Leu at its carboxy terminus. Support for this limitation is found in the specification at page 11, lines 24-27.

Claims 22 and 31 have been amended to recite that the KDEL receptor inhibitor protein has the amino acid sequence Lys-Asp-Glu-Leu at its carboxy terminus. Support for this limitation is found in the specification at page 11, line 25.

Claims 23 and 32 have been amended to delete redundant language.

Claims 24 and 33 have been amended to delete redundant language and to recite a trimerization domain. Support for this limitation is found in the specification at page 17, lines 14-22; and page 18, lines 5-8.

Claims 25 and 34 have been amended to recite a phospholamban protein. Support for this limitation is found in the specification at page 12, line 25.

Claims 26 and 35 have been amended to change their dependency.

Claims 28 and 37 have been amended to recite TSP3 or TSP4. Support for these limitations is found in the specification at page 12, line 24.

Claim 29 has been amended to recite that:

- the ligand sequence comprises the amino acid sequence X-Asp-Glu-Leu at the carboxy terminus of the heat shock protein. Support for this limitation is found in the specification at page 11, lines 24-27.

- the KDEL receptor inhibitor is a protein. Support for this limitation is found in the specification at page 5, lines 11-14.

- the KDEL receptor inhibitor protein comprises the amino acid sequence X-Asp-Glu-Leu located at the carboxy terminus of the KDEL receptor inhibitor protein. Support for this limitation is found in the specification at page 11, lines 24-27.

Claims 44 and 45 recite that the pentamerization domain is selected from the group consisting of: SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:7. Support for these limitations is found in the specification at page 13, lines 6-11 (SEQ ID NOs:1 and 2); page 13, lines 24-25 (SEQ ID NO:7).

Claims 46 and 47 recite that the trimerization domain is selected from the group consisting of: SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, and SEQ ID NO:6. Support for these limitations is found in the specification at page 13, lines 12-23.

Claims 48 and 49 recite that the KDEL receptor inhibitor protein is selected from the group consisting of: SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, and SEQ ID NO:34. Support for these limitations is found at Figure 1B (SEQ ID NO:13), Figure 2B (SEQ ID NO:15), Figure 3B (SEQ ID NO:17), Figure 4B (SEQ ID NO:19), Figure 5B (SEQ ID NO:21), Figure 6B (SEQ ID NO:23), Figure 7B (SEQ ID NO:25), Figure 8B (SEQ ID NO:27), Figure 9B (SEQ ID NO:29), and Figure 10B (SEQ ID NO:34).

Claim 50 recites that the protein is naturally produced by the cell. Support for this limitation is found in the specification at page 5, line 15.

Claim 51 recites that the protein is expressed as a result of the introduction of a nucleic acid encoding the protein into the cell. Support for this limitation is found in the specification at page 5, lines 15-16.

Claims 52 and 57 recite introducing a nucleic acid encoding the KDEL receptor inhibitor protein into the cell. Support for this limitation is found in the specification at page 14, lines 28-29.

Claims 53 and 59 recite that the method includes introducing the KDEL receptor inhibitor protein into the cell in microvesicles. Support for this limitation is found in the specification at page 14, line 29.

Claims 54 and 60 recite that the method includes linking the KDEL receptor inhibitor protein to a sugar residue, folate, insulin, or transferrin. Support for these limitations is found in the specification at page 15, lines 8-9.

Claims 55 and 61 recite that the the KDEL receptor inhibitor protein is conjugated to polyethylene glycol or an antigenic peptide. Support for these limitations is found in the specification at page 16, lines 14-16.

Claim 56 recites introducing a nucleic acid encoding the protein into the cell. Support for this limitation is found in the specification at page 20, lines 1-3.

Claim 58 recites introducing a nucleic acid encoding the heat shock protein into the cell. Support for this limitation is found in the specification at page 21, lines 26-27.

Claim 62 recites that the antigenic peptide is associated with an infectious disease or cancer. Support for these limitations is found in the specification at page 20, lines 19-20.

Claim 63 recites that the cancer is a sarcoma, lymphoma, leukemia, melanoma, carcinoma of the breast, carcinoma of the prostate, ovarian carcinoma, carcinoma of the cervix, uterine carcinoma, colon carcinoma, carcinoma of the lung, glioblastoma, or astrocytoma. Support for these limitations is found in the specification at page 20, lines 21-23.

Claim 64 recites that the infectious disease is caused by a bacterium, virus, protozoan, mycoplasma, fungus, yeast, parasite or prion. Support for these limitations is found in the specification at page 20, lines 25-26.

Claim 65 recites that the virus is a human papilloma virus, a herpes virus, a retrovirus, a hepatitis virus, an influenza virus, a rhinovirus, a respiratory syncytial virus, a cytomegalovirus, or an adenovirus. Support for these limitations is found in the specification at page 20, line 28 to page 21, line 2.

Claim 66 recites that the retrovirus is human immunodeficiency virus 1 or 2. Support for these limitations is found in the specification at page 20, line 29.

Claim 67 recites that the bacterium is a bacterium of the genus Salmonella, Staphylococcus, Streptococcus, Enterococcus, Clostridium, Escherichia, Klebsiella, Vibrio, or Mycobacterium. Support for these limitations is found in the specification at page 21, lines 2-3.

Claim 68 recites that the antigenic peptide is associated with a defective tumor suppressor gene. Support for this limitation is found in the specification at page 20, lines 23-24.

Claim 69 recites that the defective tumor suppressor gene is p53. Support for this limitation is found in the specification at page 20, line 24.

Claim 70 recites that the antigenic peptide is associated with an oncogene. Support for this limitation is found in the specification at page 20, line 24.

Claim 71 recites that the oncogene is ras, src, erbB, fos, abl, or myc. Support for these limitations is found in the specification at page 20, lines 24-25.

Claims 72 and 73 recite that X in the amino acid sequence X-Asp-Glu-Leu is selected from the group consisting of: Lys, His, and Asp. Support for these limitations is found in the specification at page 11, line 25 (Lys); page 11, line 25 (His); and page 25, line 10 (Asp).

Claims 74 and 75 recite a nucleotide sequence selected from the group consisting of: SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, and SEQ ID NO:35. Support for these limitations is found at Figure 1C-D (SEQ ID NO:14), Figure 2C-D (SEQ ID NO:16), Figure 3C-D (SEQ ID NO:18), Figure 4C-D (SEQ ID NO:20), Figure 5C-D (SEQ ID NO:22), Figure 6C-D (SEQ ID NO:24), Figure 7C-D (SEQ ID NO:26), Figure 8C-D (SEQ ID NO:28), Figure 9C-D (SEQ ID NO:30), and Figure 10C-D (SEQ ID NO:35).

In the Preliminary Amendment dated October 26, 2000, the specification was amended to insert sequence identifiers in numerous places. The Examiner requested clean copies of these amended pages. Accordingly, the Applicants herewith provide substitute pages 2-28 to replace original pages 2-27. The substitute pages are identical to the original pages except for the insertion of the sequence identifiers. Thus, the substitute pages do not introduce new matter.

The objections

The Examiner requested that clean copies of the specification pages that were amended in the Preliminary Amendment dated October 26, 2000 be submitted. Such clean copies are enclosed herewith.

Claims 20 and 29 were objected to as being unclear. These claims have been amended along the lines suggested by the Examiner.

The rejections under 35 U.S.C. §112

I. Enablement

Claims 20-37 were rejected under 35 U.S.C. §112 for lack of enablement, although the Examiner did state that the specification was enabling for the use of polynucleotides of SEQ ID NOs: 14, 16, 18, 20, 22 24, 26, 28, 30, and 35 as well as for polynucleotides encoding

the proteins set forth in SEQ ID NOs: 13, 15, 17, 19, 21, 23, 25, 27, 29, and 34. The enablement rejection was based on the view that the claims cover a broad range of secreted proteins, HSP/antigen complexes, and KDEL receptor inhibitors having a broad range of oligomerization domains and KDEL receptor binding regions and that the disclosure in the specification is not commensurate with the broad scope of these claims because there is allegedly a lack of predictability between changes in the amino acid sequence of the recited secreted proteins, HSP/antigen complexes, and KDEL receptor inhibitors and their function. Therefore, according to the Examiner, the specification must provide detailed guidance as to the effect of particular changes in amino acid sequence on function and the specification fails to provide such guidance. See, e.g., page 4, line 19 to page 5, line 8 of the Office Action, where it is stated that:

> Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired KDELr inhibitor activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function.

See also page 6, line 18 to page 7, line 4, where it is stated that:

> The specification does not support the broad scope of Claims 20-37 because the specification does not establish: (A) regions of the secreted protein, or HSP, KDELr binding domain structure which may be modified without effecting the activity of said proteins to bind to KDELrs; (B) regions of the protein structure which may be modified without affecting the activity of the KDELr inhibitors; (C) the general tolerance of the activity of the KDELr inhibitors to modification and extent of such tolerance; (D) a rational and predictable scheme for modifying any residues with an expectation of obtaining the desired biological function; and (E) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Claims 27 and 36 have been canceled without prejudice. Claims 20-26, 28-35, and 37 have been amended without prejudice to the Applicants' right to refile and prosecute these claims in their form prior to the present amendments in possible continuing applications. Amended claims 20-26, 28-35, and 37 now recite that the secreted protein, the heat shock protein, and the KDEL receptor inhibitor are proteins that have the amino acid sequence X-Asp-

Glu-Leu at their carboxy termini. New claims 44-75 share these limitations. For the following reasons, the Applicants submit that the enablement rejection should not apply to amended claims 20-26, 28-35, and 37, or to new claims 44-75.

A. Predictability of biological activity

Based on the passages quoted above from the Office Action, the enablement rejection was premised, at least in part, on the view that changing the amino acid sequence of a secreted protein, a heat shock protein, or a KDEL receptor inhibitor protein anywhere in the protein might be expected to have a significant impact on the function of the protein. Therefore, the specification must provide detailed instructions as to exactly where and how the amino acid sequence of the protein may be changed and still preserve function (see, e.g., the second quote above, where the specification is faulted because it does not teach "a rational and predictable scheme for modifying any residues with an expectation of obtaining the desired biological function").

The Examiner's argument is based on the erroneous assumption that changing the amino acid sequence of the claimed proteins anywhere (e.g., outside of the regions of the oligomerization domain and the X-Asp-Glu-Leu sequence) would affect the function of the proteins. This assumption is erroneous because the recited oligomerization domains and X-Asp-Glu-Leu sequences are modular. They are amino acid sequences which are able to carry out their function irrespective of the larger context into which they are placed. In other words, they are sufficient to independently confer upon the protein in which they are found the characteristics of oligomerization and KDEL receptor binding, no matter what the amino acid sequence of the other parts of the protein. This is borne out by many publications that report the engineering of oligomerization domains and X-Asp-Glu-Leu sequences into a wide variety of different proteins. In these cases, the oligomerization domains and X-Asp-Glu-Leu sequences confer the desired properties upon the protein into which they have been engineered, viz., oligomerization or ability to bind KDEL receptors, despite the great differences in amino acid sequence of the proteins into which the oligomerization domains and X-Asp-Glu-Leu sequences have been engineered. This is discussed further below.

i. X-Asp-Glu-Leu sequences

X-Asp-Glu-Leu sequences, as well as their modular nature, were well known in the art at the time of filing of the parent of the present application. It was recognized that these sequences could be appended to the carboxy terminus of a wide variety of protein or peptides and would still function to cause the retention of those proteins or peptides in the endoplasmic reticulum. For example:

• Wilson et al., 1993, J. Biol. Chem. 268:7465-7468[1] synthesized a variety of peptides having an XDEL sequence at their carboxy termini. These peptides, despite differences in their N-terminal sequences, were capable of being retained in the endoplasmic reticulum due to the presence of the XDEL sequences at their carboxy termini. The authors concluded that the XDEL sequence is sufficient to confer this function on proteins in which it appears at the carboxy terminus. See at page 7468, left column:

> The tetrapeptide sequence KDEL, or a closely related sequence, is found at the carboxyl terminus of soluble ER proteins and some membrane proteins. This sequence is both necessary and sufficient to ensure the retention of such proteins in the ER lumen despite the high rate of forward vesicular transport to the Golgi complex and subsequent organelles of the secretory pathway. [emphasis added; footnote and citations omitted]

• Kim et al., 1998, Proc. Natl. Acad. Sci. USA 95:2997-3002 described the recombinant linkage of a Lys-Asp-Glu-Leu sequence to the B subunit of Shiga toxin in order to increase the retention of the toxin in the endoplasmic reticulum.

• Townsley et al., 1993, EMBO J. 12: 2821-2829 described the His-Asp-Glu-Leu sequence.

• Lewis & Pelham, 1992, Cell 68:353-364 described the recombinant linkage of the Lys-Asp-Glu-Leu, His-Asp-Glu-Leu, and Asp-Asp-Glu-Leu sequences to lysozyme.

---

[1] Copies of this and other publications referred to herein are included with the Information Disclosure Statement filed herewith.

The specification expressly discloses and teaches the use of three members of the X-Asp-Glu-Leu sequence family: Lys-Asp-Glu-Leu (see page 11, lines 25-26), His-Asp-Glu-Leu (see page 11, line 26), and Asp-Asp-Glu-Leu (see page 25, lines 10-11). The specification also provides many examples of the Lys-Asp-Glu-Leu sequence recombinantly linked to an oligomerization domain (see Figures 1-10). In addition, the specification defines the "X" in the X-Asp-Glu-Leu sequence as being limited to amino acids (see page 11, line 25), which limits the number of species within the generic term "X-Asp-Glu-Leu sequence." Moreover, the specification discloses how these species can be tested for binding to the KDEL receptor (see page 12, lines 2-5).

Given the modular nature of X-Asp-Glu-Leu sequences, the widespread knowledge of X-Asp-Glu-Leu sequences in the art, the examples of X-Asp-Glu-Leu sequences taught in the specification, combined with the limited number of species encompassed by the term "X-Asp-Glu-Leu sequence," the breadth of the term "X-Asp-Glu-Leu sequence" is reasonably correlated with the teachings of the specification combined with the knowledge of the art. Thus, the recitation of this term in the present claims is enabled.

ii. Oligomerization domains

The modular nature of oligomerization domains, such as trimerization domains and pentamerization domains, was well known in the art at the time of filing of the parent of the present application. It was recognized that oligomerization domains could be linked to a wide variety of proteins or peptides and would still function properly. For example:

- McCoy et al., 1997, EMBO J. 16:6230-6236 showed that the 30 amino acid long oligomerization domain of p53 could fold independently of the rest of the p53 protein and thus could form dimers and tetramers even in the absence of nearly all of the other amino acids naturally found in the p53 sequence.

- Hüttelmaier et al., 1997, Eur. J. Biochem. 247:1136-1142 recombinantly linked oligomerization domains from vinculin with the unrelated maltose binding protein and showed that the fusion proteins so formed were capable of oligomerization.

•Song et al., 1997, J. Biol. Chem. 272:4398-4403 disclosed that amino acid residues 135-178 of caveolin-1 constituted an oligomerization domain that could be recombinantly linked to the glutathione S-transferase protein, resulting in a fusion protein capable of oligomerization.

• Jousset et al., 1997, EMBO J. 16:69-82 conducted swapping experiments in which the TEL oligomerization domain was exchanged for oligomerization domains from ETS-1, ERG-2, and GABPα to form recombinant proteins capable of oligomerization.

• Orlinick et al., 1997, J. Biol. Chem. 272:32221-32229 localized the ability of Fas ligand to form trimers to a 47 amino acid domain in the extracellular portion of the protein.

• Efimov et al., 1994, FEBS Lett. 341:54-58 showed that a recombinantly expressed N-terminal fragment (a pentamerization domain) from rat cartilage oligomeric matrix protein could form pentamers similar to those of the native protein.

• Terskikh et al., 1997, Proc. Natl. Acad. Sci. USA 94:1663-1668 disclosed a fusion gene in which a pentamerization domain was recombinantly linked to a peptide capable of binding a mouse lymphoma Ig idiotype. See Figure 2, page 1665, right column.

In addition to oligomerization domains being well known in the art, the specification provides many examples of oligomerization domains. See, for example:

• rat COMP (SEQ ID NO:1) (see page 13, lines 6-8)

• human COMP (SEQ ID NO:2) (see page 13, lines 9-11)

• mouse TSP3 (SEQ ID NO:3) (see page 13, lines 12-14)

• human TSP3 (SEQ ID NO:4) (see page 13, lines 15-17)

• human TSP4 (SEQ ID NO:5) (see page 13, lines 18-20)

• Xenopus TSP4 (SEQ ID NO:6) (see page 13, lines 21-23)

• human PLB (SEQ ID NO:7) (see page 13, lines 24-25)

Given the widespread knowledge of oligomerization domains in the art and the many examples of oligomerization domains taught in the specification, the breadth of the term "oligomerization domain" is reasonably correlated with the teachings of the specification

combined with the knowledge of the art. Thus, the recitation of this term in the present claims is enabled.

One skilled in the art would find it routine to choose a suitable oligomerization domain for use in the claimed methods from the many known in the art or taught in the specification. Standard techniques of recombinant engineering could then be used to recombinantly link the oligomerization domain to an X-Asp-Glu-Leu sequence, if so desired. Because of their modular natures, it would be expected that these recombinantly linked oligomerization domains and X-Asp-Glu-Leu sequences would function properly. It would then be a simple matter to test whether the resulting protein is capable of oligomerization by following the guidance at page 14, lines 20-22 of the specification where a method is disclosed which would allow one to test in vitro whether the protein is capable of forming oligomers. That the oligomers function as KDEL receptor inhibitors could be easily tested by methods described in the application. See the specification at page 18, line 22 to page 19, line 1, which teaches an in vivo method of determining whether the oligomers can promote the secretion of proteins which normally tend to bind to the KDEL receptor and be retained in the cell. See also the specification at page 19, lines 2-13, which teaches an in vitro method of determining whether the oligomers bind to KDEL receptors. Still another such method is found in the specification beginning at page 24, line 23 ("2. Testing the ability of of KDEL receptor inhibitor to bind to KDEL receptor").

II. Written description

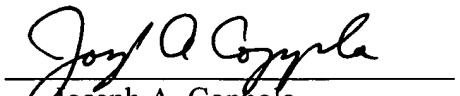
Claims 20-37 were rejected for lack of an adequate written description because the claims encompass a genus of KDELr binding motifs and a genus of KDELr inhibitors while the specification allegedly fails to describe sufficient characteristics of these genera and fails to identify sufficient numbers of species within these genera such that a skilled artisan would recognize that the Applicants were in possession of these genera. See the Office Action at page 7, line 20 to page 8, line 7. Claims 27 and 36 have been canceled. Amended claims 20-26, 28-35, and 37, as well as new claims 44-75, recite secreted proteins, heat shock proteins, and KDEL

receptor inhibitors that are proteins and that have in common well known, well defined domains (oligomerization domains and X-Asp-Glu-Leu sequences) that are used extensively in the art. Thus, the recitation of these domains serves to define a genus of nucleic acids having common, well defined, well understood characteristics. Moreover, the specification provides ten species within the genus of KDEL receptor inhibitors. This conveys to one skilled in the art that the Applicants were in possession of the claimed invention. Therefore, it is requested that this rejection be withdrawn.

The time for responding to the Office Action was set for December 16, 2002. Enclosed herewith is a Petition for the Extension of Time under 37 C.F.R. § 1.136(a) for a period sufficient to permit the filing of this response.

The Applicants hereby make a Conditional Petition for any relief available to correct any defect seen in connection with this filing, or any defect seen to be remaining in this application after this filing. The Commissioner is authorized to charge Kenyon & Kenyon's Deposit Account No. 11-0600 for the Petition fee and any other fees required to effect this Conditional Petition.

Respectfully submitted,



Joseph A. Coppola
Reg. No. 38,413

Attorney for Applicants
KENYON & KENYON
One Broadway
New York, NY 10004
(212) 425-7200 (telephone)
(212) 425-5288 (facsimile)

Date: February 18, 2003

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims:

20. (amended) A method of increasing the secretion of a protein by a cell, wherein the protein comprises a ligand sequence which binds to a KDEL receptor, wherein the ligand sequence comprises the amino acid sequence X-Asp-Glu-Leu (SEQ ID NO:38) at the carboxy terminus of the protein, the method comprising exposing the cell to a KDEL receptor inhibitor protein at a concentration which increases the secretion of the protein from the cell relative to the secretion of the protein in the absence of the KDEL receptor inhibitor protein, wherein the KDEL receptor inhibitor protein comprises the amino acid sequence X-Asp-Glu-Leu (SEQ ID NO:38) located at the carboxy terminus of the KDEL receptor inhibitor protein.

21. (amended) The method of claim 20, wherein the KDEL receptor inhibitor protein is an oligomeric KDEL receptor inhibitor protein comprising a plurality of protein subunits, wherein each subunit comprises an oligomerization domain and has, at its carboxy terminus, [a region which binds to a KDEL receptor] the amino acid sequence X-Asp-Glu-Leu (SEQ ID NO:38).

22. (amended) The method of claim [21] 20, wherein the [region of the KDEL receptor inhibitor protein which binds to a KDEL receptor] amino acid sequence X-Asp-Glu-Leu (SEQ ID NO:38) at the carboxy terminus of the protein has the amino acid sequence Lys-Asp-Glu-Leu (SEQ ID NO:37).

23. (amended) The method of claim 21, wherein the oligomerization domain [of the KDEL inhibitor protein] is a pentamerization domain.

24. (amended) The method of claim 21, wherein the oligomerization domain [of the KDEL inhibitor protein] is a [pentamerization] trimerization domain.

25. (amended) The method of claim 23, wherein the pentamerization domain is derived from a cartilage oligomeric matrix protein or a phospholamban protein.

26. (amended) The method of claim [21] 24, wherein the trimerization domain is derived from a thrombospondin protein.

28. (amended) The method of claim [22] 26, wherein the [oligomerization domain is derived from a] thrombospondin protein is TSP3 or TSP4.

29. (amended) A method for promoting the release of a heat shock protein/antigenic peptide complex from a cell, where the heat shock protein [contains] comprises a ligand sequence which binds to a KDEL receptor, where the ligand sequence comprises the amino acid sequence X-Asp-Glu-Leu (SEQ ID NO:38) at the carboxy terminus of the heat shock protein, the method comprising exposing the cell to a KDEL receptor inhibitor protein at a concentration which increases the secretion of the complex from the cell relative to the secretion of the complex in the absence of the KDEL receptor inhibitor protein, where the KDEL receptor inhibitor protein comprises the amino acid sequence X-Asp-Glu-Leu (SEQ ID NO:38) located at the carboxy terminus of the KDEL receptor inhibitor protein.

30. (amended) The method of claim 29, wherein the KDEL receptor inhibitor protein is an oligomeric KDEL receptor inhibitor protein comprising a plurality of protein subunits, wherein each subunit comprises an oligomerization domain and has, at its carboxy terminus, [a region which binds to a KDEL receptor] the amino acid sequence X-Asp-Glu-Leu (SEQ ID NO:38).

31. (amended) The method of claim [30] 29, wherein the [region of the KDEL receptor inhibitor protein which binds to a KDEL receptor] amino acid sequence X-Asp-Glu-Leu (SEQ ID NO:38)

at the carboxy terminus of the protein has the amino acid sequence Lys-Asp-Glu-Leu (SEQ ID NO:37).

32. (amended) The method of claim 30, wherein the oligomerization domain [of the KDEL inhibitor protein] is a pentamerization domain.

33. (amended) The method of claim 31, wherein the oligomerization domain [of the KDEL inhibitor protein] is a [pentamerization] trimerization domain.

34. (amended) The method of claim 32, wherein the pentamerization domain is derived from a cartilage oligomeric matrix protein or a phospholamban protein or a phospholamban protein.

35. (amended) The method of claim [30] 33, wherein the trimerization domain is derived from a thrombospondin protein.

37. (amended) The method of claim [31] 35, wherein the [oligomerization domain is derived from a] thrombospondin protein is TSP3 or TSP4.